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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/719,870 | 04/12/2001 | Masad J. Damha | 1770-206US FC | 5859 |

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| EXAMINER | |
|---|---|
| EPPS FORD, JANET L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/719,870 | DAMHA ET AL. | |
| | Examiner | Art Unit | |
| | Janet L. Epps-Ford | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2,7-17,36 and 43-46* is/are pending in the application.

4a) Of the above claim(s) *7-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,36 and 43-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☑ All b)☐ Some * c)☐ None of:

1.☑ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-02-2006 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claim 1 (cancelled), 2 (pending), 3-6 (cancelled), 7-17 (are withdrawn), 18-35 (cancelled), 36 (pending), 37-42 (cancelled), 43-46 are currently pending.

4. Claims 2, 36, and 43-46 are currently under examination. Claims 7-17 are withdrawn.

### *Response to Amendment*

### *Claim Rejections - 35 USC § 102*

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claim 2, 36, and 43-46 are rejected under 35 U.S.C. 102(a) as being anticipated by Wilds et al.

Wilds et al. disclose 2'F-arabino-β-D-arabinofuranosyl oligonucleotides in solution (see page 300 (General Methods and Figure 1). These oligonucleotides are disclosed as functioning to elicit RNase H activity when bound to single stranded RNA, and to form triplex structures (see Summary on page 303).

7. Claims 2, 36 and 44-45 remain rejected under 35 U.S.C. 102(b) as being anticipated by Kois et al. (SEE IDS of 5-15-2002, Nucleosides & Nucleotides, Vol. 12., No. 10., pages 1093-1109), or Kois et al. (SEE IDS of 5-15-2002, Nucleic acids Symposium Series, 1993, No. 29, pages 215-216.)

Applicants traverse the instant rejection on the grounds that based upon Applicant's amendment to the claims to recite: "consisting of" instead of *based on,* the instant amendment obviates this rejection. Contrary to Applicant's assertions, it remains that the claims are rejected over the cited references since the claims are not limited to the preventing or modulating of any particular gene, are not limited to a specific nucleobase sequence, and because the reference discloses oligonucleotides that are uniformly modified with 2'-deoxy-2'-fluoro-β-D-arabinonucleotide modifications, see for example, Table 1, oligomers 5 and 6. The oligomers are disclosed in a 5μM solution in buffers A-C, absent evidence to the contrary, at least buffer B may serve as pharmaceutically acceptable carrier. In regards to the poly FMAU sequence of oligomer #5, absent evidence to the contrary, the oligonucleotide would be expected to hybridize in a sequence specific manner to the poly(A) tail of any mRNA, and thereby potentially modulate the processing of the mRNA, and thereby modulate or prevent the expression of the mRNA. Furthermore, in regards to the functional language "wherein said

oligonucleotide is capable to hybridize to complementary RNA and induce (Rnase-H)-mediated cleavage thereof," recited in claim 45, since the oligonucleotide structures of Kois et al. (both references) meet all the structural limitations recited in the claims, absent evidence to the contrary, the oligonucleotides of Kois et al. would also be expected to have the same functional properties as Applicant's claimed oligonucleotides.

***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. Claims 2, 36, and 43-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Manoharan et al. (US Patent No. 6,369,209 B1).

Manoharan et al. disclose oligonucleotides that are disclosed as useful in therapeutic and investigative purposes. The oligonucleotides of this reference are also

disclosed as having modifications that will increase affinity and nuclease resistances while concurrently serving as substrates for RNAse H when bound to a target RNA strand.

A preferred aspect of the oligonucleotides of this reference includes wherein the nucleotides are modified for eliciting RNAse H, specifically wherein the nucleotides are arabinonucleotides having 2'-deoxy-2'-cyano, 2'-deoxy-2'-fluoro, 2'-deoxy-2'-chloro, 2'-deoxy-2'-bromo, 2'-deoxy-2'-azido, 2'-methoxy and the unmodified arabinonucleotides that include a 2'-OH.

Col. 21, lines 23-50 of Manoharan et al. recites:

The oligonucleotides of the invention can be used in diagnostics, therapeutics and as research reagents and kits. They can be used in pharmaceutical compositions by including a suitable pharmaceutically acceptable diluent or carrier. They further can be used for treating organisms having a disease characterized by the undesired production of a protein. The organism should be contacted with an oligonucleotide having a sequence that is capable of specifically hybridizing with a strand of nucleic acid coding for the undesirable protein. Treatments of this type can be practiced on a variety of organisms ranging from unicellular prokaryotic and eukaryotic organisms to multicellular eukaryotic organisms. Any organism that utilizes DNA-RNA transcription or RNA-protein translation as a fundamental part of its hereditary, metabolic or cellular control is susceptible to therapeutic and/or prophylactic treatment in accordance with the invention. Seemingly diverse organisms such as bacteria, yeast, protozoa, algae, all plants and all higher animal forms, including warm-blooded animals, can be treated.

Further, each cell of multicellular eukaryotes can be treated, as they include both DNA-RNA transcription and RNA-protein translation as integral parts of their cellular activity. Furthermore, many of the organelles (e.g., mitochondria and chloroplasts) of eukaryotic cells also include transcription and translation mechanisms. Thus, single cells, cellular populations or organelles can also be included within the definition of organisms that can be treated with therapeutic or diagnostic oligonucleotides.

Moreover, Example 67 of this reference describes the synthesis of 2'-fluoro-β-D-arabinofuranosyl oligonucleotides.

***Claim Rejections - 35 USC § 103***

10. Claims 2, 36 and 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (US Patent No. 5,646,126) in view of Wilds et al.

11. This rejection was inappropriately withdrawn by the examiner in the Office Action of 9-26-05. Upon further consideration, as noted above, Wilds et al. applies as prior art under 35 USC 102(a). Therefore, it is considered that the following rejection should not have been withdrawn.

Cheng et al. describe oligonucleotides comprising 2'-deoxy, 2'-fluoro or 2'-difluoro nucleosides, wherein between 8 and 18 of said nucleosides are linked consecutively, see Figure 1, formula 2, see also claim 1. Specifically, the compounds of Cheng et al. encompasses wherein the R1 and R2 substituents of the 2' position of the nucleosides comprises either H or F, or wherein both R1 and R2 are F (fluorine) see col. 63, lines 24-25. Additionally, Cheng et al. teach that ODNs (oligonucleotides)

including α and β arabinosides, are included within the scope of the invention (col. 9, lines 33-39).

Cheng et al. does not specifically disclose isolated oligonucleotides comprising arabinose sugars and 2'-fluoro or 2'-difluoro modified nucleosides consecutively linked in the same molecule.

Wilds et al. disclose 2'F-arabino-β-D-arabinofuranosyl oligonucleotides in solution (see page 300 (General Methods and Figure 1). These oligonucleotides are disclosed as functioning to elicit RNase H activity when bound to single stranded RNA, and to for triplex structures (see Summary on page 303). Wilds et al. also teach that these oligonucleotides have increased nuclease resistance in comparison to DNA, and enhanced stability in comparison to DNA and RNA, see page 303.

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the oligonucleotides of Cheng et al. with the teachings of Wilds et al. to produce the compositions of the present invention. It would have been obvious to modify the oligonucleotides of Cheng et al. to comprise 2'-difluoro or 2'-fluoro arabinosyl nucleosides because, Cheng et al. expressly teach that their disclosed invention encompasses oligonucleotides comprising or including α and β arabinosides. Moreover, one of ordinary skill in the art seeking to enhance the properties of an oligonucleotide would have been motivated to modify the teachings of Cheng et al. to design the compounds of the present invention because Wilds et al. teach that oligonucleotide stability can be increased by introducing 2'-deoxy-2'-β-D-fluoro-arabinofuranosyl nucleosides into the oligonucleotide structure. One of ordinary skill in

the art would have had a reasonable expectation of success in designing the compounds according to the present invention, since Wllds et al. describes the synthetic steps necessary for introducing 2'-deoxy-2'-fluoro-arabinofuranosyl moieties into an oligonucleotide structure.

Therefore, the invention as a whole would have been *prima facie* obvious over Cheng et al. in view of Wilds et al.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Janet L. Epps-Ford
Primary Examiner
Art Unit 1633

*JLE*